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Dr Donald J. Woodward

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Dept of Physiology and Pharmacology
Wake Forest University
Medical Center Boulevard
Winston-Salem, NC 27157-1083 AFOSR-PR-04 0175

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13. ABSTRACT (Maximum 200 words)
The overall goal of the "University Initiative" project "Neostriatal Neuronal Activity and Behavior" was to establish a new technical approach for the study of ensembles of single neurons in CNS during tasks requiring sensory motor integration. An aim was to establish methodology for chronic implant of arrays of recording electrodes in rat neostriatum and other regions. Instrumentation was to be developed to allow amplification and spike sorting to be done for up to 64 concurrent spike trains. An acquisition system was to record the time events of spike trains, stimuli, and behavior events for up to four days continuously. An analysis capability was to provide a wide range of standard analysis procedures including histograms and rasters. A new approach for neuron ensemble analysis was to be developed to deal with statistical fluctuations of ensemble patterned activity across trials. Experimental studies were to study neuronal population activity during a series of tasks including tone and treadmill locomoting and a delayed matching-to-sample task with a spatial memory requirement. Computational simulation was to be done to explore short-term

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memory properties of the local circuitry between medium spiny neurons in neostriatum. Development of the experimental approach was the primary goal. Extended experimental analysis was secondary for this type of developmental project.

FINAL TECHNICAL REPORTApproved for public release;
distribution unlimited.**RE: Air Force Award S49620-92-J-30/****"Neostriatal Neuronal Activity and Behavior"****Donald J. Woodward, Ph.D., Principal Investigator****GOALS:**

The overall goal of the "University Initiative" project "Neostriatal Neuronal Activity and Behavior" was to establish a new technical approach for the study of ensembles of single neurons in CNS during tasks requiring sensory motor integration. An aim was to establish methodology for chronic implant of arrays of recording electrodes in rat neostriatum and other regions. Instrumentation was to be developed to allow amplification and spike sorting to be done for up to 64 concurrent spike trains. An acquisition system was to record the time events of spike trains, stimuli, and behavior events for up to four days continuously. An analysis capability was to provide a wide range of standard analysis procedures including histograms and rasters. A new approach for neuron ensemble analysis was to be developed to deal with statistical fluctuations of ensemble patterned activity across trials.

Experimental studies were to study neuronal population activity during a series of tasks including tone and treadmill locomoting and a delayed matching-to-sample task with a spatial memory requirement. Computational simulation was to be done to explore short-term memory properties of the local circuitry between medium spiny neurons in neostriatum. Development of the experimental approach was the primary goal. Extended experimental analysis was secondary for this type of developmental project.

PROGRESS:

Major progress has occurred toward the stated Goals. Populations of up to fifty simultaneous single neuron spike trains can now be recorded in rat neostriatum during awake behaviors. A typical study might record a population of 20-30 neurons during each experimental session. A recent study, for example, obtained spike train data from populations of 20 neurons during a reaction time task in which the rat nose pokes, remains still for .5 to 2.5 sec and withdraws rapidly (200-300 msec) after a tone cue. After 300-600 trials, the rat was placed on a treadmill where a CS+ tone cued the treadmill onset and a CS- tone was presented for alternate 30 sec locomotion and 30 sec

rest during the treadmill off-state for a 60-minute test period. Ten daily sessions were conducted to allow behavior correlates of neurons to be studied over time to establish stability of the activity over time. Many of the same neurons were recorded over ten sessions across both tasks.

An initial publication in Nature (1) has described the changes in population response which appears within rat thalamus after anesthesia of the skin under a whisker. The results revealed an immediate alteration in receptive field response of the population in which reduction of the receptive field center is accompanied with an enhancement of responses in the surrounding area. A parallel report in the recordings of the National Academy of Sciences (2) further describes population responses in rat thalamus. Responses describing the "receptive fields" within thalamic neuron populations show dramatic shifts in time after the stimulus. The result of study of the population vector reveal the moment-to-moment fluctuations of the transfer characteristics of the system.

A different type of approach has shown that single neuron spike trains can be recorded over long-term behaviors where this has not been previously feasible. For example, a study of ventral neostriatum activity has shown that this region contains neurons which code phasic activity during the behavioral sequences leading up to drug self-administration. The nucleus accumbens has been postulated to play a major role in "reinforcement," yet direct recording of neuronal activity revealed a role more accurately described as the "Sequencing of a motor strategy" (3).

Studies are in progress to characterize the distribution of responses in dorsal neostriatum during a delayed match/nonmatch-to-sample task. The initial experience with this paradigm has revealed that neurons specific to "learning the sample" exist in parallel with others that code more for match/nonmatch-to-sample. Computational simulation (4,5) has shown that the reciprocal inhibition of neighboring medium spiny neurons leads to activity-dependent persistent states. This can function as a form of working or short-term memory. Groups of medium spiny neurons can serve as binary memory devices to assemble information arriving asynchronously from cortex. Convergence from the neostriatum to pallidum would allow graded signals to be coded by summation of binary signals in the medium spiny neurons. In effect, the neostriatum may function as an array of D/A converters. This form of analysis provides a framework of simulation/theory upon which to base future experimental work.

The development of this new experimental approach was done in cooperation

with Dr. John Chapin, Hahnemann University in Pennsylvania and Dr. Sam Deadwyler at Bowman Gray School of Medicine. The three-laboratory coordination proved indispensable for this effort. Our efforts helped establish the commercial viability of Spectrum Scientific (Mr. Harvey Wiggins), Dallas, Texas, a commercial vendor of the critical spike sorter instrumentation. Many other laboratories have developed plans for this type of research. Instrumentation has been acquired or ordered by Drs. J. Houk, B. Peterson, B. Llinas, M. Merzenich, and G. Gerstein. There may be soon up to 25 laboratories adopt the approach. Dr. Mountcastle, who pioneered studies of cortex and of population recordings, in a recent lecture at the Society for Neuroscience, referred to the Nature article (1) as "one of the most promising advances in thalamo cortical neurophysiology in over a decade." This view, if widespread, may account for the rapid acceptance of our contribution.

ARTICLES PUBLISHED:

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2. Nicolelis MAL, Lin RCS, Woodward DJ, Chapin JK. Peripheral block of ascending cutaneous information induces immediate spatio-temporal changes in thalamic networks. *Proc Natl Acad Sci* 1993; 90(6): 2212-2216.
3. Chang J-Y, Sawyer SF, Lee R-S, Woodward DJ. Electrophysiological and pharmacological evidence for the role of the nucleus accumbens in cocaine self-administration in freely moving rat. *J Neurosci* 1994; in press
4. Kirillov AB, Myre CD, Woodward DJ. Bistability, switches and working memory in a two-neuron inhibitory-feedback model. *Biol Cybernetics* 1993; 68:441-449.
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